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(54) Abstract Title

Electrostatic application of powder material to solid dosage forms

(57) An apparatus for electrostatically applying a powder material to a solid dosage form includes a source 1 of charged powder material, a support assembly 2 for supporting the solid dosage form 3 with a front face in the vicinity of the source of powder material and facing the source of powder material, the support assembly 2 including an electrically conducting member 5 in the vicinity of the rear face of the solid dosage form and an electrically conducting shield 8 disposed closely around the solid dosage form 3 between the front face and the rear face of the solid dosage form, and means 4 for creating a potential difference between the source of powder material and the electrically conducting member and for maintaining the electrically conducting shield at a potential more similar to that of the source of powder material than to that of the electrically conducting member.

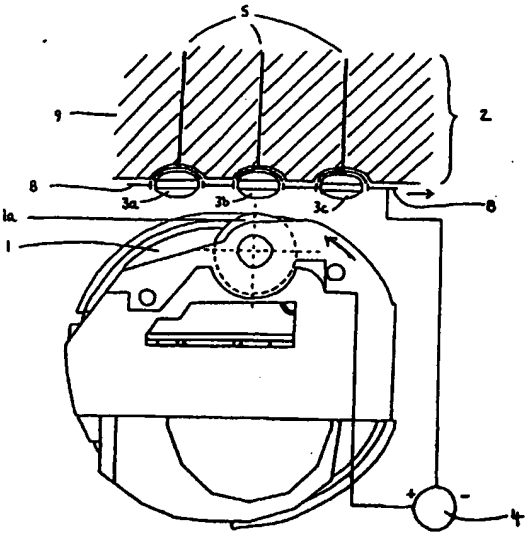

Figure 1

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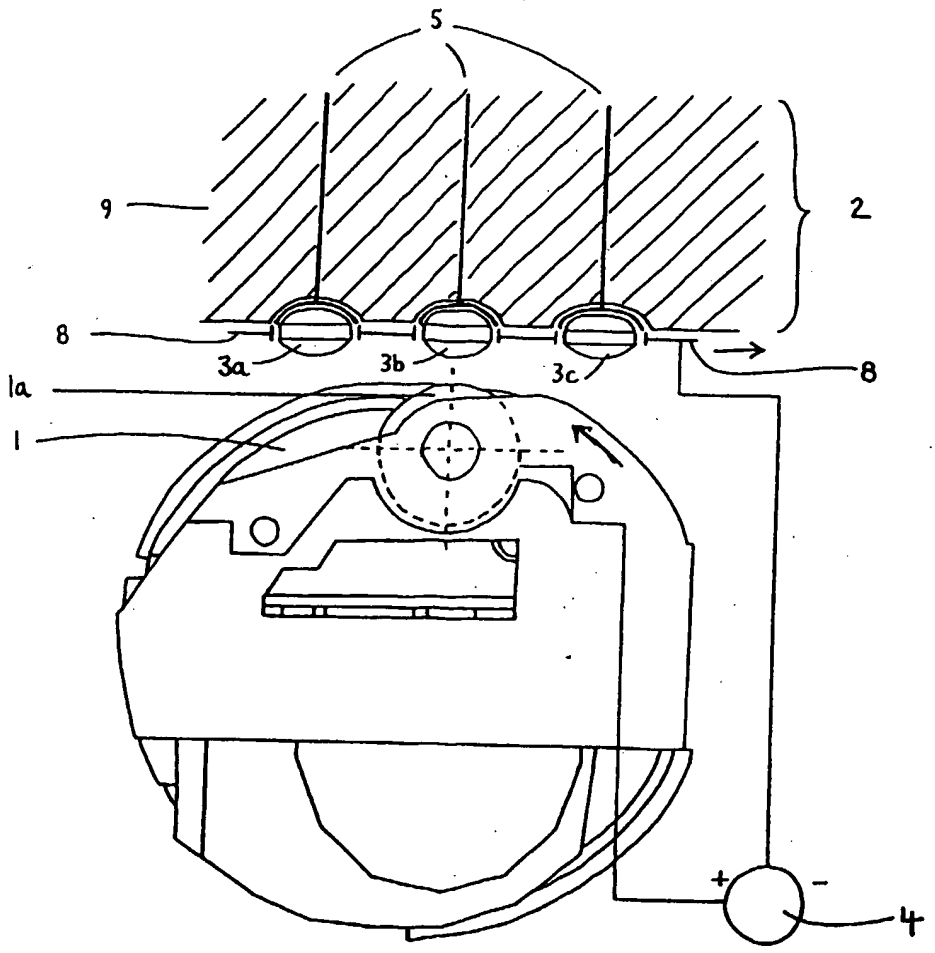

FIGURE 1

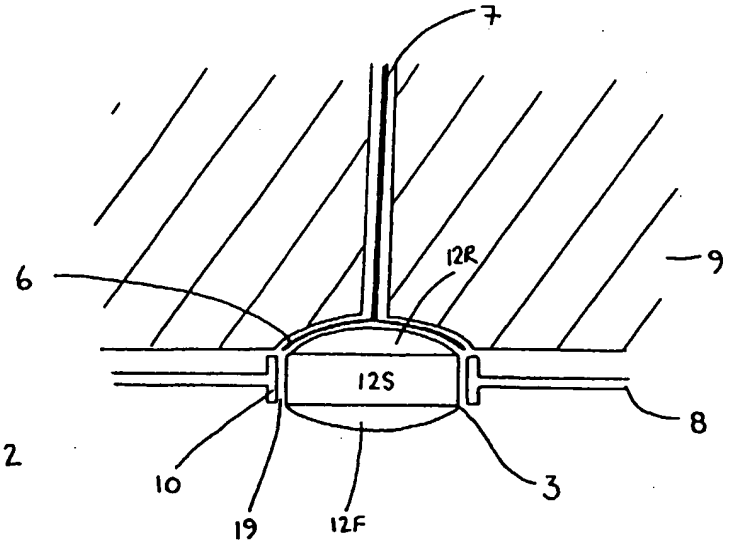

FIGURE 2

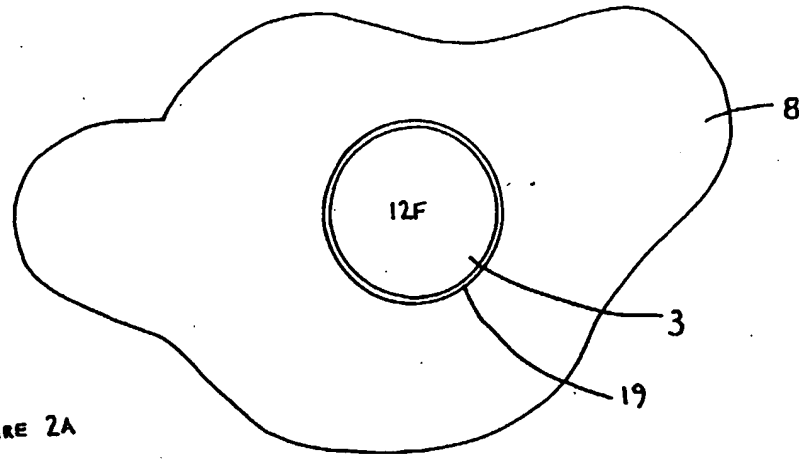

FIGURE 2A

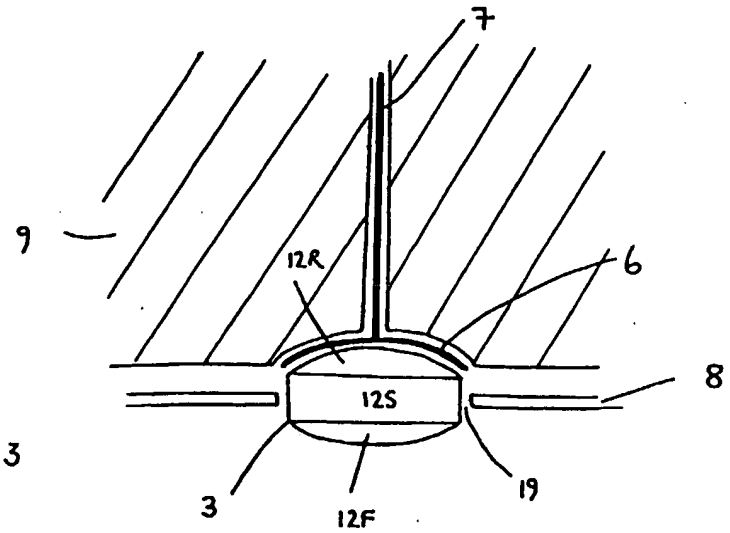

FIGURE 3

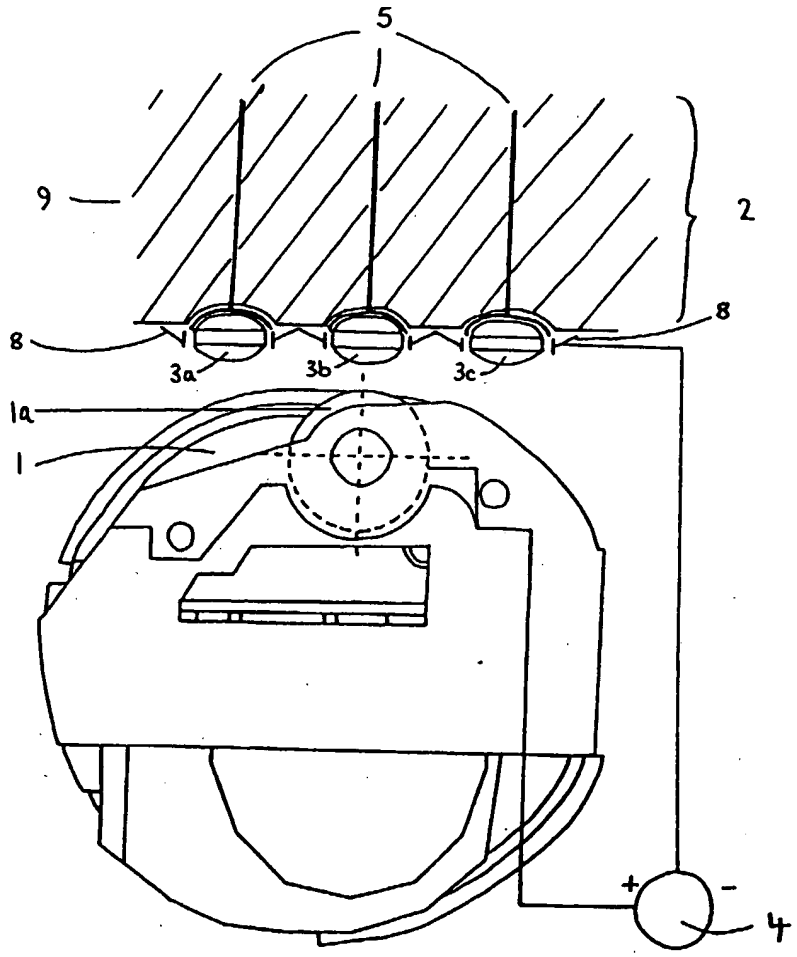

FIGURE 4A

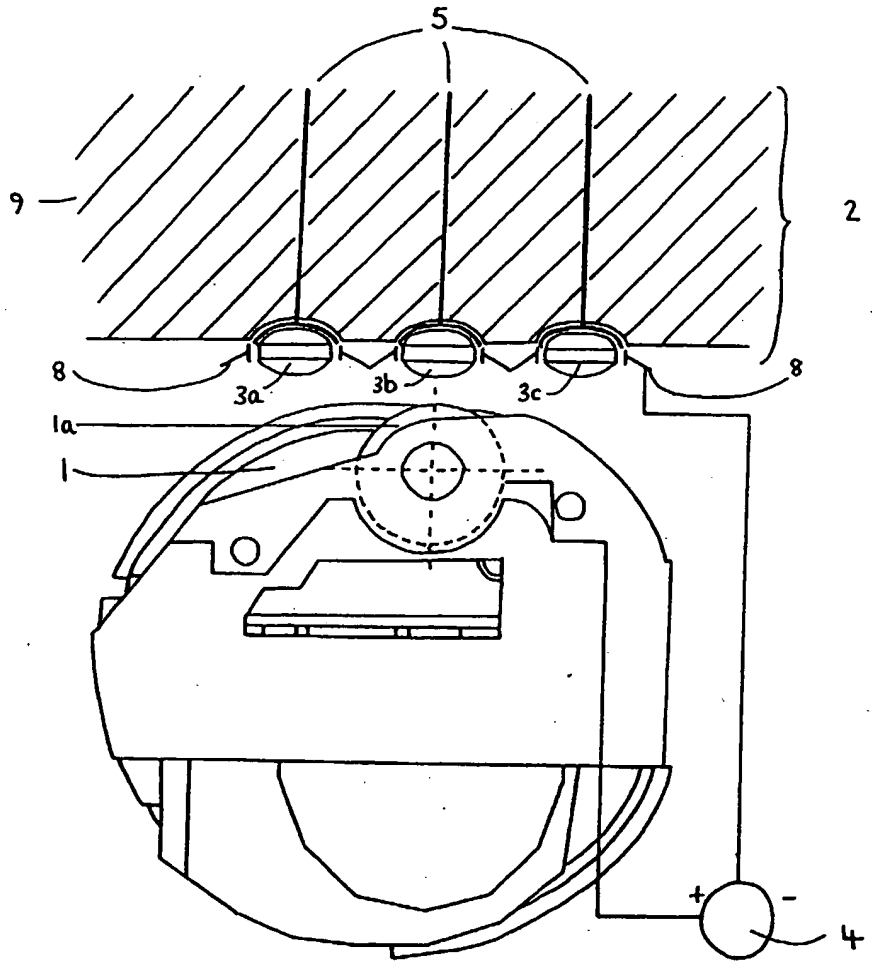

FIGURE 4B

Electrostatic Application of Powder Material to Solid Dosage Forms

The present invention relates to a method and apparatus for the electrostatic application of powder material onto the surfaces of solid dosage forms, and more particularly, but not exclusively, pharmaceutical solid dosage forms.

A "solid dosage form" can be formed from any solid material that can be apportioned into individual units; it may be, but is not necessarily, an oral dosage form. Examples of pharmaceutical solid dosage forms include pharmaceutical tablets, pharmaceutical pessaries, pharmaceutical bougies and pharmaceutical suppositories. The term "pharmaceutical tablet" should be interpreted as covering all pharmaceutical products which are to be taken orally, including pressed tablets, pellets, capsules and spherules. Examples of non-pharmaceutical solid dosage forms include items of confectionery and washing detergent tablets.

The electrostatic application of powder material to solid dosage forms is known. In one technique, described in WO 96/35516 powder material is applied onto pharmaceutical tablets while the tablets are moving on a drum past a source of the powder material. The tablets are supported in cupped receptacles on a first drum and all the exposed areas of the tablets are coated as they pass the

source of powder material. Subsequently the tablets are transferred onto a second drum where they are supported again in cupped receptacles but in the opposite orientation to that on the first drum so that areas of the tablets not exposed on the first drum are now exposed and *vice versa*. In that way the whole of each tablet is coated following its passage around both drums.

When using the apparatus of WO 96/35516 we have found that some powder is applied to the surface of the drum as well as to the tablet. That is wasteful of powder and also makes cleaning of the apparatus time consuming, especially if the powder being applied by the apparatus is to be charged. The coating of the sides of the tablets using the apparatus of WO 96/35516 can also be somewhat arbitrary: portions of the sides are liable to be exposed during coating on each of the drums and may therefore acquire more powder than the ends of the tablets; on the other hand, the amount of powder reaching the sides of the tablets may be limited so that even after both coating stages relatively little powder is applied to the sides of the tablet. Also, it is sometimes desired to coat only one half of the tablet (one end and part of the side wall) and in that case it is desirable to have a well defined edge to the coating. It is difficult to provide such a coating with a well defined edge using the apparatus of WO 96/35516.

According to the invention there is provided an apparatus for electrostatically applying a powder material to a solid dosage form, the apparatus including

a source of charged powder material,

a support assembly for supporting the solid dosage form with a front face in the vicinity of the source of powder material and facing the source of powder material, the support assembly including an electrically conducting member in the vicinity of the rear face of the solid dosage form and an electrically conducting shield disposed closely around the solid dosage form between the front face and the rear face of the solid dosage form, and

means for creating a potential difference between the source of powder material and the electrically conducting member and for maintaining the electrically conducting shield at a potential more similar to that of the source of powder material than to that of the electrically conducting member.

We have found that, by providing an electrically conducting shield closely around the solid dosage form and maintaining the shield at a potential more similar to that of the source of powder material than to that of the electrically conducting member, a physical and electrostatic barrier can be created and it becomes possible both to confine the application of powder to the solid dosage form and to coat a forward part of the solid

dosage form uniformly as far as a limit defined by the shield, with substantially no coating taking place to the rear of the shield. Thus, a well defined limit to the coating can be obtained.

There can be one or more gaps in the shield extending around the solid dosage form, but it is preferred that the shield extends continuously around all of the solid dosage form.

The shape of the opening defined by the shield, in which opening the solid dosage form is revceived, is preferably selected according to the shape of the solid dosage form, with the shield conforming to the outline shape of the solid dosage form as seen when viewed from the source of powder material. Often that outline shape will be circular and in that case the shield preferably defines a circular opening, but it will be appreciated that other outline shapes are also possible, including, for example, an oval shape, in which case the shield preferably defines an oval opening. The shield may extend outwardly away from the vicinity of the solid dosage form. The shield preferably has a cylindrical part defining a cylindrical opening for accommodating the solid dosage form. The cylindrical opening may be of circular cross-section but, as explained above, may also have other cross-sectional shapes, for example an oval shape. The shield may consist substantially entirely of the cylindrical part. An

advantage of limiting the shield to a cylindrical part closely surrounding the solid dosage form is that it reduces the effect of the shield on the electric field between the powder source and the solid dosage form. Ideally the shield would have no discernible effect on that field, although in practice some effect is most likely to be discernible. The length of the cylindrical part of the shield may be relatively long, but it is preferred that the length is less than the depth of the solid dosage form, measured as the maximum separation between the front and rear faces of the solid dosage form; furthermore it is preferred that the length is substantially shorter than said depth of the solid dosage form; preferably the length is less than one third of said depth.

The provision of an electrically conducting member closely surrounding the solid dosage form over a significant area is liable to provide a degree of capacitative coupling between the shield and the solid dosage form which in turn is not desirable. Reducing the length of the shield reduces that coupling. Another feature that serves to reduce that effect is for the part of the shield immediately adjacent to the solid dosage form to have a thickness of less than 2 mm, preferably less than 1 mm. Such a small thickness may be provided by tapering of a member which may then be much thicker away from the solid dosage form, but preferably the shield is made of

sheet metal. It is also preferred that the end portion of the shield adjacent to the solid dosage form and closest to the source of powder material is parallel to the side surfaces of the solid dosage form, providing a constant spacing between the end portion of the shield and the solid dosage form. It is also preferred that the edge of the end portion of the shield is at a constant spacing from the source of powder material.

In the case where the shield extends outwardly away from the vicinity of the solid dosage form it may extend radially, but alternatively it may extend outwardly in a direction inclined to a radial direction. The angle of inclination is preferably in the range of from 30 degrees to 60 degrees and may be of the order of 45 degrees. The inclination may be in a forwards direction (towards the powder source) with increasing radial distance from the solid dosage form or it may be in a rearwards direction (away from the powder source) with increasing radial distance from the solid dosage form. In the case where the inclination is in a forwards direction it is preferred that the forwardmost portions of the shield do not project forwardly as far as the forwardmost portion of the solid dosage form.

In order to improve the effectiveness of the shield as both a physical and electrical barrier, it is preferred that when, in use, the solid dosage form is supported on

the support assembly, there is a gap of not more than about 1 mm, and preferably less than 1 mm, between the solid dosage form and the shield. The gap is preferably uniform around the whole of the circumference of the solid dosage form.

Preferably the electrically conducting shield comprises an electrically conducting element covered by a layer of insulating material. The provision of a layer of insulating material, which is preferably thin, prevents accidental electrical contact being made between the solid dosage form and the shield.

Preferably the electrically conducting member is adjacent to the rear face of the solid dosage form. It is not essential for the electrically conducting member to make contact with the solid dosage form but it is preferable for it to be in contact with the rear face of the solid dosage form. Preferably the electrically conducting member includes a shaped receiving portion for receiving the rear face of the solid dosage form with the rear face conforming closely to the receiving part over a major part of the area of the rear face. For example in the case where the rear face of the solid dosage form is convex, the receiving portion preferably has a corresponding concave shape.

Usually the apparatus will be arranged for applying powder material to a plurality of solid dosage forms. Thus

the support assembly is preferably suitable for supporting a plurality of solid dosage forms and preferably includes a plurality of electrically conducting members, each in the vicinity of a rear face of a respective one of the solid dosage forms, and a plurality of electrically conducting shields, each disposed closely around a respective one of the solid dosage forms between the front face and the rear face of the respective solid dosage form.

Preferably the support assembly is mounted for movement relative to the source of charged powder material. That enables each of the solid dosage forms to pass the source of charged powder material. The support assembly may comprise a drum rotatable about a horizontal axis, as illustrated in WO 96/35516. An alternative arrangement is to provide a body which is movable, in a translational and/or rotational movement along a path which is preferably confined to a single plane, which may be horizontal or may be inclined at an angle of up to 65 degrees to the horizontal. For example the body may travel along an endless horizontal path. The source of charged powder material may be provided above or below the horizontal path.

Preferably the means for creating a potential difference between the source of powder material and the electrically conducting member comprises a voltage source for applying a bias voltage between the source of powder material and the

electrically conducting member. The invention may also be applied, however, to a case where the potential difference between the powder source and the electrically conducting member is created only by the charge on the powder, which may even be applied to the powder at a location remote from the electrically conducting member. Conveniently, the means for creating a potential difference between the source of powder material and the electrically conducting member and the means for maintaining the electrically conducting shield at a potential more similar to that of the source of powder material than to that of the electrically conducting member are provided by a single voltage source.

According to the invention there is also provided a method of electrostatically applying a powder material to a solid dosage form, the method including the steps of

providing a source of charged powder material,

supporting a solid dosage form on a support assembly with a front face in the vicinity of the source of powder material and facing the source of powder material, the support assembly including an electrically conducting member in the vicinity of the rear face of the solid dosage form and an electrically conducting shield disposed closely around the solid dosage form between the front face and the rear face of the solid dosage form,

creating a potential difference between the source of powder material and the electrically conducting member and maintaining the shield at a potential more similar to that of the source of powder material than to that of the electrically conducting member, whereby powder material is applied to the solid dosage form forward of the shield but substantially not rearward of the shield.

The powder material may be electrostatically charged in any suitable way. For example, it may be charged triboelectrically.

The solid dosage form may be a domed tablet having a pair of opposite domed end faces joined by a cylindrical side wall. In such a case, the electrostatically charged powder material may be applied uniformly over the whole of one domed end face of the tablet and a forward part of the cylindrical side wall, the remaining, rearward, part of the cylindrical side wall being shielded from the application of powder by the shield. The solid dosage form may, more particularly, be an oral dosage form and/or a pharmaceutical dosage form, for example a pharmaceutical tablet.

The step of creating a potential difference between the source of powder material and the electrically conducting member of the support assembly may comprise the step of providing an electrically conducting roller at the powder source and applying a potential difference between the

electrically conducting member of the support assembly and the electrically conducting roller at the powder source.

The potentials at which the electrically conducting shield and the source of powder material (preferably the electrically conducting roller) are preferably of the same sign and may be substantially the same.

The electrically conducting member may be electrically charged (to a potential substantially different and preferably of opposite sign to the powder source), but is preferably maintained at earth potential.

The potential difference created between the source of powder material and the electrically conducting member preferably includes a bias voltage that is a steady DC voltage. The polarity of the bias voltage is chosen according to whether the powder is positively or negatively charged, which in turn is dependent upon the powder and/or the charging process employed: for negatively charged powders the bias voltage is negative and for positively charged powders it is positive, the bias voltage being defined as positive when the potential at the source of powder material is greater than the potential at the solid dosage form and *vice versa*. Preferably an alternating voltage, which is preferably substantially higher than the DC voltage, is superimposed on the initial bias voltage. The presence of such an alternating voltage serves to mobilise the charged powder reducing any tendency of the

powder particles to adhere to a surface on which they are carried; in a described embodiment that surface is the periphery of a roller. The alternating voltage preferably has a peak to peak value greater than, and more preferably more than twice, the peak value of the DC bias voltage. For example the alternating voltage may have a peak to peak value of the order of 5kV. The sum of the DC bias voltage and one half of the peak to peak alternating voltage must not be so great that the potential difference causes breakdown of the air. The frequency of the alternating voltage is preferably in the range of 1 to 15kHz.

Preferably a plurality of solid dosage forms are supported on the support assembly, the support assembly including a plurality of electrically conducting members, each in the vicinity of a rear face of a respective one of the solid dosage forms, and a plurality of electrically conducting shields, each disposed closely around a respective one of the solid dosage forms between the front face and the rear face of the respective solid dosage form, and the support assembly is moved relative to the source of charged powder material to bring in turn the front faces of the solid dosage forms into the vicinity of the source and facing the source.

Preferably, the method further comprises the step of treating the powder material to fix it on the solid dosage form. The treatment of the powder material to fix it to

the solid dosage form preferably involves a heating step, preferably using infra red radiation, but other forms of heating such as convection, conduction or induction may be used. The powder material should be heated to a temperature above its softening point, and then allowed to cool until solid. It is important to control the amount of heat applied to avoid degradation of the powder material and/or the solid dosage form. The amount of heat required may be reduced by applying pressure to the powder material. Alternatively, the powder material may include a polymer which is cured during the treatment, for example, by irradiation with energy in the gamma, ultra violet or radio frequency bands.

The method may comprise the step of applying powder material to a first surface of the solid dosage form, and the subsequent step of applying powder material to a second surface of the solid dosage form. Where the method is being used to apply a continuous coating to a solid dosage form, such a step will usually be necessary if the whole surface of the dosage form is to be coated. The apparatus and method employed for applying powder material to the second surface may be similar to the apparatus and method employed for applying powder material to the first surface. Indeed the powder material may be applied to the second surface by passing the solid dosage form through the same apparatus a second time. It may be preferred, however, for

the apparatus to differ from that employed for applying powder material to the first surface. For example, in the case of a domed pharmaceutical tablet, the application of powder material to an end face of the tablet may change the electrical properties of the tablet. For example the layer of applied powder material may be more electrically insulating than the material of the tablet core which may then make it desirable to increase capacitive coupling between the tablet and the electrically conducting member of the support assembly.

Preferably, the method is carried out as a continuous process.

The method of the present invention is not restricted to the use of any particular type of powder material. The powder materials described in WO 96/35413 are examples of suitable powder materials.

The powder material may include a biologically active material, that is, a material which increases or decreases the rate of a process in a biological environment. The biologically active material may be one which is physiologically active.

Conventionally, where an active material is to be administered in solid dosage form, the active material is mixed with a large volume of non-active "filler" material in order to produce a dosage form of manageable size. It has been found, however, that it is difficult to control

accurately the amount of active material contained in each dosage form, leading to poor dose uniformity. That is especially the case where the required amount of active material in each dosage form is very low.

By electrostatically applying active material to a dosage form, it has been found to be possible to apply accurately very small amounts of active material to the dosage form, leading to improved dose reproducibility.

The powder material comprising active material may be applied to a solid dosage form containing the same or a different active material, or may be applied to a solid dosage form containing no active material. It should be understood that where reference is made to the solid dosage form being a pharmaceutical tablet, the term "pharmaceutical tablet" is to be taken as including a tablet core which contains no active material but is to have active material applied in the powder material. It should be understood that features described above with reference to the method of the invention may also, where appropriate be present in the apparatus of the invention and *vice versa*. Thus, for example, the apparatus may include one or more solid dosage forms and the dosage forms may be domed tablets as described above.

By way of example certain embodiments of the invention will now be described with reference to the accompanying drawings, in which:

Fig. 1 is a schematic sectional view of an apparatus for electrostatically applying a powder material to a solid dosage form;

Fig. 2 is an enlarged sectional view of a part of the apparatus;

Fig. 2a is a schematic plan view of the part of the apparatus shown in Fig. 2;

Fig. 3 is an enlarged sectional view of a modified form of the part of the apparatus shown in Fig. 2;

Fig. 4a is a schematic sectional view of another apparatus for electrostatically applying a powder material to a solid dosage form; and

Fig. 4b is a schematic sectional view of yet another apparatus for electrostatically applying a powder material to a solid dosage form.

Referring firstly to Figs. 1, 2 and 2a, the apparatus shown generally comprises a source 1 of electrostatically charged powder material, a support assembly 2 for supporting tablets 3 and a voltage source 4. The support assembly 2 supports a plurality of tablets and in Fig. 1 three of the tablets 3a, 3b and 3c are shown.

The source 1 of charged powder material includes a roller 1a that is electrically conducting and is connected to the voltage source 4. Powder material in the source 1

is fed to the roller 1a and is charged triboelectrically during its passage to the roller 1a.

The support assembly 2 defines a plurality of tablet receiving stations at each of which a respective tablet 3a, 3b, 3c is received. At each station there is an electrically conducting member 5 which includes a cupped receiving part 6, on which the tablet rests, and a stem part 7. The support assembly 2 includes an electrically conducting shield 8 mounted (by suitable mounts not shown) just above an electrically insulating body 9 of the assembly 2. The shield is coated with a layer of electrically insulating material. The shield 8 has openings 19 within each of which a respective tablet 3 is received with the shield closely surrounding but spaced from the tablet 3 by a small distance (for example 0.5mm) as shown in Fig. 2a. The shield 8 has cylindrical portions 10 of circular cross-section which define the openings 19.

Each tablet 3 has a pair of opposite domed end faces, namely a front face 12F and a rear face 12R, and also a cylindrical side wall 12S, as shown in Fig. 2. The cupped receiving part 6 of the electrically conducting member 5 is shaped so that its concave lower face matches the convex rear face 12R of the tablet 3.

It will be noted that in Fig. 1 the tablet is shown on a bottom face of the support assembly 2. It should be understood that the tablet is held on the bottom face

against the force of gravity by suitable means, for example by suction (for example, by providing air passageways through the cupped receiving parts 6 and around the stem parts 7 of the conducting members 5 and connecting those passageways to the air inlet side of a vacuum pump).

The voltage source 4 applies a bias voltage to the roller 1a of the source 1 of the charged powder material and also applies the same voltage to the shield 8. The electrically conducting member 5 is earthed. The bias voltage applied by the source 4 is a steady DC bias voltage with an AC voltage superimposed thereon.

In operation of the apparatus, the tablets 3 are moved past the source 1 of electrostatically charged powder material. In Fig. 1 the tablet 3b is shown passing the roller 1a, (with the roller 1a and the tablet moving in the directions shown by the arrows in Fig. 1). The bias voltage generates an electric field between the roller 1a and the receiving part 6 of the electrically conducting member 5. That electric field causes electrostatically charged powder at the roller 1a to be transferred across to the tablet and to coat the part of the tablet that projects forwards (downwards in Figs. 1 and 2) beyond the cylindrical portion 10 of the shield 8. The shield 8, however, provides a barrier to the powder material, preventing coating of more rearward parts of the tablet. More particularly, the shield 8 provides a physical

barrier, because of its proximity to the side wall of the tablet, and also an electrostatic barrier, being at the same voltage potential as the roller 1a. Thus, the electric field, which provides the driving force for the charged powder, will be cancelled out at some point between the powder source and the shield and will be reversed in the immediate vicinity of the shield. Powder will be repelled from approaching the shield by virtue of the voltage potential of the shield and the charge on the powder.

The description above is concerned with the part of the powder coating process in which the powder is actually applied to the tablet, that being the distinctive part of the process. It will be understood, however, that there will usually be other steps in the process including in particular a step of heating the powder to fuse it and secure it to the tablet. In a case where opposite faces of a tablet are to be coated powder may be applied to the first face, that powder fused, the tablet turned over and then powder applied to the second face and fused. Further details of other steps in the process that may be employed are given in WO 96/35516, the contents of which is incorporated herein by reference. Whilst that specification shows one particular form of support assembly for supporting and conveying the tablets, it should be understood that other systems could be used. Examples of

other conveying arrangements are shown in WO 98/20861 and WO 98/20863, the contents of which are also incorporated herein by reference. Another possible conveying arrangement is one in which the tablets are conveyed along a path disposed in a single plane (which may be horizontal or inclined), travelling through various treatment stations arranged along the path. For example, powder may be applied to one face of the tablet at a first station, the powder fused at a second station, the tablet cooled at a third station, the tablet turned over at a fourth station, powder applied to the opposite face of the tablet at a fifth station, that powder fused at a sixth station and the tablet cooled at a seventh station. Suitable powder coating materials for coating the tablets are described in WO 96/34513, the contents of which is incorporated herein by reference.

Whilst Figs. 1, 2 and 2a describe one particular shield arrangement for applying powder to a tablet, it should be understood that the shield may take any of a wide variety of forms. For example Fig. 3 shows an arrangement that is the same as that shown in Figs. 1, 2 and 2a but in which the shield 8 is in the form of a flat metal sheet with circular openings 19 within which the tablets 3 are received. The shield of Fig. 3 has the advantage that there is relatively little capacitance between the shield and each tablet 3 because only the edge of the sheet is

close to the tablet. Fig. 4a shows an arrangement similar to that of Fig. 3, but in this case the shield 8 is inclined upwardly and radially outwardly from each tablet. Fig. 4b shows a similar arrangement to that of Fig. 4a but in this case the shield 8 is inclined downwardly and radially outwardly from each tablet. It will be understood that other shapes of shield can also be adopted.

In the illustrated embodiments the body 9 is described as electrically insulating, but it is also possible for the body 9 to be electrically conducting, provided that it is insulated from the shield 8. If the body 9 is electrically conducting, then there is no longer a need to provide the separate electrically conducting members 5.

Whilst in the described embodiment the shield 8 and the roller 1a are maintained at the same potential and connected to the same voltage source, that need not be the case. For example, the shield 8 could be maintained at a potential of the same polarity as, but a different (typically smaller) magnitude from, the potential of the roller 1a. The potential at which the shield 8 is maintained may also be made adjustable to enable the effect of the shield on the coating of the tablet to be altered.

Claims

1. An apparatus for electrostatically applying a powder material to a solid dosage form, the apparatus including

a source of charged powder material,

a support assembly for supporting the solid dosage form with a front face in the vicinity of the source of powder material and facing the source of powder material, the support assembly including an electrically conducting member in the vicinity of the rear face of the solid dosage form and an electrically conducting shield disposed closely around the solid dosage form between the front face and the rear face of the solid dosage form, and

means for creating a potential difference between the source of powder material and the electrically conducting member and for maintaining the electrically conducting shield at a potential more similar to that of the source of powder material than to that of the electrically conducting member.

2. An apparatus according to claim 1, in which the shield extends continuously around all of the solid dosage form.

3. An apparatus according to claim 1 or 2, in which the shield defines a substantially circular opening for accommodating the solid dosage form.

4. An apparatus according to any preceding claim, in which the shield extends outwardly away from the vicinity of the solid dosage form.

5. An apparatus according to any preceding claim, in which the shield has a cylindrical part defining a cylindrical opening for accommodating the solid dosage form.

6. An apparatus according to claim 5, in which the length of the cylindrical part of the shield is less than the depth of the solid dosage form, measured as the maximum separation between the front and rear faces of the solid dosage form.

7. An apparatus according to any preceding claim, in which the part of the shield immediately adjacent to the solid dosage form has a thickness of less than 2 mm.

8. An apparatus according to claim 7, in which the part of the shield immediately adjacent to the solid dosage form has a thickness of less than 1 mm.

9. An apparatus according to any preceding claim, in which the shield is made of sheet metal.

10. An apparatus according to any preceding claim, in which the shield extends outwardly away from the solid dosage form in a direction inclined to a radial direction.

11. An apparatus according to claim 10, in which the angle of inclination is in the range of from 30 to 60 degrees.

12. An apparatus according to any preceding claim, in which when, in use, the solid dosage form is supported on the support assembly, there is a gap of not more than about 1 mm between the solid dosage form and the shield.

13. An apparatus according to any preceding claim, in which the electrically conducting shield comprises an electrically conducting element covered by a layer of insulating material.

14. An apparatus according to any preceding claim, in which the electrically conducting member is adjacent to the rear face of the solid dosage form.

15. An apparatus according to claim 14, in which the electrically conducting member is in contact with the rear face of the solid dosage form.

16. An apparatus according to claim 14 or 15, in which the electrically conducting member includes a shaped receiving part for receiving the rear face of the solid dosage form with the rear face conforming closely to the receiving part over a major part of the area of the rear face.

17. An apparatus according to any preceding claim, in which the potentials at which the electrically conducting shield and the source of powder material are arranged to be maintained are of the same sign.

18. An apparatus according to claim 17, in which the potentials at which the electrically conducting shield and

the source of powder material are arranged to be maintained are substantially the same.

19. An apparatus according to any preceding claim, in which the electrically conducting member is arranged to be maintained at earth potential.

20. An apparatus according to any preceding claim, in which the support assembly is suitable for supporting a plurality of solid dosage forms and includes a plurality of electrically conducting members, each in the vicinity of a rear face of a respective one of the solid dosage forms, and a plurality of electrically conducting shields, each disposed closely around a respective one of the solid dosage forms between the front face and the rear face of the respective solid dosage form.

21. An apparatus according to claim 20, in which the support assembly is mounted for movement relative to the source of charged powder material.

22. An apparatus according to any preceding claim, in which the means for creating a potential difference between the source of powder material and the electrically conducting member comprises a voltage source for applying a bias voltage between the source of powder material and the electrically conducting member.

23. An apparatus according to claim 22, in which the means for creating a potential difference between the source of powder material and the electrically conducting member and

the means for maintaining the electrically conducting shield at a potential more similar to that of the source of powder material than to that of the electrically conducting member are provided by a single voltage source.

24. A method of electrostatically applying a powder material to a solid dosage form, the method including the steps of

providing a source of charged powder material,

supporting a solid dosage form on a support assembly with a front face in the vicinity of the source of powder material and facing the source of powder material, the support assembly including an electrically conducting member in the vicinity of the rear face of the solid dosage form and en electrically conducting shield disposed closely around the solid dosage form between the front face and the rear face of the solid dosage form,

creating a potential difference between the source of powder material and the electrically conducting member and maintaining the shield at a potential more similar to that of the source of powder material than to that of the electrically conducting member, whereby powder material is applied to the solid dosage form forward of the shield but substantially not rearward of the shield.

25. A method according to claim 24, in which the solid dosage form is a domed tablet having a pair of opposite domed end faces joined by a cylindrical side wall.

26. A method according to claim 25, in which the electrically conducting shield is disposed closely around the cylindrical side wall, powder material being applied to the part of the side wall forward of the shield but not to the part of the side wall rearward of the shield.

27. A method according to any of claims 24 to 26, in which the solid dosage form is an oral dosage form.

28. A method according to any of claims 24 to 27, in which the solid dosage form is a pharmaceutical dosage form.

29. A method according to claim 28, in which the pharmaceutical dosage form is a pharmaceutical tablet.

30. A method according to any of claims 24 to 29, in which the potentials at which the electrically conducting shield and the source of powder material are maintained are of the same sign.

31. A method according to claim 30, in which the potentials at which the electrically conducting shield and the source of powder material are maintained are substantially the same.

32. A method according to any of claims 24 to 31, in which the electrically conducting member is maintained at earth potential.

33. A method according to any of claims 24 to 32, in which the potential difference created between the source of powder material and the electrically conducting member includes a bias voltage that is a steady DC voltage.

34. A method according to claim 33, in which an alternating voltage is superimposed on the DC voltage.

35. A method according to claim 34, in which the alternating voltage has a peak to peak value that is more than twice the DC voltage.

36. A method according to any of claims 24 to 35, in which a plurality of solid dosage forms are supported on the support assembly, the support assembly including a plurality of electrically conducting members, each in the vicinity of a rear face of a respective one of the solid dosage forms, and a plurality of electrically conducting shields, each disposed closely around a respective one of the solid dosage forms between the front face and the rear face of the respective solid dosage form, and the support assembly is moved relative to the source of charged powder material to bring in turn the front faces of the solid dosage forms into the vicinity of the source and facing the source.

37. A method according to any of claims 24 to 36, further comprising the step of treating the powder material to fix it on the solid dosage form.

38. A method according to claim 37, in which the treatment of the powder material to fix it on the solid dosage form includes a heating step.

39. A method according to any of claims 24 to 38, comprising the step of applying powder material to a first

surface of the solid dosage form and the subsequent step of applying the material to a second surface of the solid dosage form.

40. A method according to any of claims 24 to 39, in which the powder material includes a biologically active material.

INVESTOR IN PEOPLE

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Claims searched:	1-40	**Date of search:**	17 June 2002

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UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

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Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
A	JP 2001-212479	(TOKAI) See the figures and the WPI abstract. Note charged mask 24.	-

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

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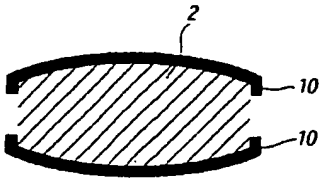

(57) Abstract: A pharmaceutical dosage form comprising: a) a tablet core comprising a pharmaceutically active ingredient and one or more pharmaceutically active ingredient and one or more pharmaceutically acceptable adjuvants, the tablet core having a tensile strength of less than 38 N/cm^2 before coating and fusion and b) a coating extending over at least 25% of the surface area of the tablet core, the coating resulting from deposition of a powder comprising fusible particles and fusing the particles to form a coating film, thereby providing the pharmaceutical dosage form with a greater hardness/crush strength than the tablet core. The tablet core may be formed by light compression with enables coated components and fragile components, such as capsules, to be used within the compression blend with little or no damage.

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PHARMACEUTICAL DOSAGE FORMS COMPRISING TABLET CORE HAVING A TENSILE STRENGTH BELOW 38 N/SQCM AND A COATING TO PROTECT THE SOFT CORE

This invention relates to pharmaceutical dosage forms and in particular to solid pharmaceutical dosage forms such as tablets with improved structural integrity.

Tablets are generally made by compressing a powder mixture under high pressure in order to form a tablet having the necessary crushing strength for the handling required during packaging and distribution. The powder mixture generally comprises a pharmaceutically active ingredient and one or more pharmaceutically acceptable adjuvants e.g. binder, diluent, disintegrant, lubricant, wetting agent, glidant, surfactant, release aid, colourant etc.

There are certain types of pharmaceutical formulations which could be conveniently administered in the form of a tablet but are not readily susceptible to conventional tableting techniques. For example, rapidly dissolving or disintegrating formulations, which are intended to disintegrate or dissolve within a few seconds, should ideally have a porous, low density structure which is not compatible with high pressure tableting techniques. Similarly, beads or microcapsules of active ingredient could be conveniently administered in the form of a tablet but they are susceptible to damage under the high pressures involved with conventional tableting techniques. When formulations are tableted using reduced pressures there may be a significant reduction in the strength of the resulting tablet which is disadvantageous and may be totally unacceptable. For example, the tablets may disintegrate during subsequent handling, storage, transport and packaging, particularly if they are loose in a container. Also, the tablets may disintegrate upon handling by the patient e.g. when extracting from a blister pack or the like.

US-A-6207199 discloses a process for making a rapidly dissolving dosage form in which a porous particulate powder matrix comprising at least two polymeric components which serve as the dosage form matrix is produced. The polymeric components have different solubilities. A pharmaceutical compound is combined with the powder and other additives may be added

and the mixture is formed in to a dosage form e.g. tablet by mild compression. Due to the porous nature of tablet, the tablet tends to be rather fragile and breakable and generally benefits from the added protection afforded by a coating. The coating may comprises a polymer, such as a polyvinyl alcohol or a polyvinylpyrrolidone which, when applied forms a polymeric net over and into the tablets. This net maintains the tablet intact but does not inhibit the capillary uptake of the tablet once placed in an aqueous environment. The polymer is applied to the tablet in solution e.g. by dropping, by spraying or by passing the tablet through an environment saturated with the coating agent. Alternatively, the tablet may be formed by a sintering process in which one or more polyethylene glycols is mixed with the drug, support matrix mixture. After forming the tablet, the tablet is heated briefly e.g. at 90°C for ten minutes. The polyethylene glycol within the mixture melts forming a thin coating on the tablet.

WO01/10418 discloses a rapidly disintegratable tablet comprising at least one active substance and a mixture of excipients which include at least one binding polymer, the tablet is sintered for a sufficient time and temperature to allow the binding polymer to change status or melt and allow the polymer to resolidify as the temperature is reduced to ambient temperature thereby providing excellent tablet binding characteristics. The preferred binding polymer is polyethylene glycol.

Membrane coated beads or microcapsules are often incorporated into hard capsules to provide immediate or controlled release dosage forms. Tablets containing these beads or microcapsules have several advantages over capsules for the speed and cost of manufacturing, and also the ability to incorporate a high amount of active ingredients. Furthermore, the beads containing tablets do not rely on the use of gelatine, which is objectionable to certain patient groups, However, compaction of beads into tablets can be frequently problematic due to core fracture and cracking of the coat, which can result in the premature release of the active material from the dosage forms.

US5780055 discloses a tablet incorporating biologically active ingredient – loaded beads and cushioning beads comprising microcrystalline cellulose, wherein the cushioning bead is prepared by extrusion-spheronisation, followed by freeze-drying, and the cushioning bead has a diameter of about 0.2 to 2.0mm. These cushioning beads exhibit both brittle fracture and plastic deformation. Both brittle fracture and plastic deformation are desired because when the cushioning beads, mixed with biologically loaded beads are compacted, initial fragmentation into primary particles not only fills the voids between the biologically active ingredient – loaded beads, but also surrounds them. Plastic deformation would then enhance the particle – particle interactions, thereby producing stronger tablets.

EP 0824344 and EP 1075838 comprise a method of coating a pharmaceutical substrate, especially a tablet core, wherein a pharmaceutically acceptable powder coating material comprising active material is electrostatically applied to a surface of the substrate, wherein the coated substrate constitutes a dosage unit; and a powder coating material suitable for use in the electrostatic powder coating of a pharmaceutical substrate, in which the material is pharmaceutically acceptable, is treatable to form a film coating and includes composite particles, the composite particles comprising two or more components having different physical and/or chemical properties, the material comprising active material.

It is stated that when the powder material is first deposited on the tablet core it is in most cases only weakly adhered to the surface of the substrate and is easily dislodged. Treatment to form a film coating is especially advantageous when coating a pharmaceutical tablet core because the core itself is likely to be of low mechanical strength and the film coating can be used to impart strength and make the coated tablets more resistant to subsequent processing such as packaging and opening of packages.

It is further stated that in the coating process disclosed therein the tablet core is handled delicately throughout the coating process so that even a fragile tablet core is not damaged and the method may be employed to coat tablet

cores that would be too fragile to withstand conventional tablet coating processes. Thus the method enables tablets of conventional shape but of a wider range of compositions to be produced; also, tablets of unconventional shapes, for example having opposite flat faces rather than conventional domed faces, may be produced by the invention. Such flat-faced tablets are generally too fragile to be coated using conventional methods.

The present invention provides an alternative pharmaceutical dosage form in which tablets having good structural integrity are obtained from a core which is formed under light compression. The structural integrity of the tablets can be measured by radial tensile strength. This is determined by diametrical compression measurement. The test can be carried out using a Schleuniger tester based on a counterweight principle. The tablet is placed between two anvils, a moving anvil driven by a speed-controlled electric motor presses the tablet against a stationary anvil. The maximal force which causes the tablet to fracture is then recorded and the radial tensile strength is calculated as follows:-

$$\sigma = 2F/D\ t\ \pi$$

where:

σ is tensile strength
F is maximal force to cause fracture during diametrical compression
D diameter
t thickness of tablet

According to the present invention there is provided a pharmaceutical dosage form comprising:

a) a tablet core comprising a pharmaceutically active ingredient and one or more pharmaceutically acceptable adjuvants, the tablet core having a tensile strength of less than 38 N/cm^2 before coating and fusion and

b) a coating extending over at least 25% of the surface area of the tablet core, the coating resulting from deposition of a powder comprising fusible particles and fusing the particles to form a coating film, thereby

providing the pharmaceutical dosage form with a greater tensile strength than the tablet core.

The invention provides a means for obtaining tablets having good structural integrity which are formed from cores having a tensile strength of less than 38 N/cm^2 (2.5kP) i.e. cores that are so weak that previously they would have been regarded as too weak for practical use. The cores may have a tensile strength less than 30 N/cm^2 (2.0kP), preferably less than 22 N/cm^2 (1.5kP). The cores may be formed by light compression and enable coated components and fragile components, such as capsules, to be used within the compression blend with little or no damage.,

While EP 0824344 and EP 1075838 disclose the robustness of tablets may be improved by electrostatic coating of powder and fusing the references do not suggest that such weak tablet cores used in the present invention may be used to form viable pharmaceutical dosage forms.

The invention provides a simple effective means of improving the structural integrity of tablet cores by partially or fully coating the tablet core with a fusible powder and fusing the powder to form a film. In addition to improving the hardness the friability weight loss is significantly improved. The coating material may be selected to be readily soluble, gradually soluble or substantially insoluble in body fluids e.g. gastric juices, saliva etc. and thus the dosage form may be constructed to provide a rapidly disintegrating product or a sustained release product by suitable selection of coating materials.

The coating extending over the tablet core results from the deposition of a powder comprising fusible particles. This technique allows the formation of a thin, continuous film over surface areas of the tablet core. In general, the film will cover from 25 to 100% preferably 50 to 100% of the surface area of the tablet core. The resulting tablet preferably has a tensile strength of at least 50 N/cm^2, 60 N/cm^2 and most preferably at least 70 N/cm^2.

The shape of the tablet core is not critical since the deposition of powder can readily be achieved over a variety of shaped bodies. The tablet core may be formed by tableting techniques e.g. compression of powder and/or granules under light compression although other techniques such as moulding may be employed. A convenient tablet core has a circular cross-section and two major opposing surfaces which may be planar, for example planar with bevelled edge, concave, convex etc. The coating may conveniently extend over the major surfaces leaving the sidewall(s) exposed. Optionally the sidewall may be partially coated with the coating.

The tablet core comprises an adjuvant and a pharmaceutically active ingredient. The tablet core has a tensile strength of less than 38 N/cm^2, preferably less than 30 N/cm^2, more preferably less than 22 N/cm^2.

Generally the adjuvant will comprise a binder. Suitable binders are well known and include acacia, alginic acid, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydroxypropylmethylcellulose, magnesium aluminium silicate, kaltodectrin, methylcellulose, polyethylene oxide, povidone, sodium alginate and hydrogenated vegetable oils.

The tablet core may comprise a release rate controlling additive. For example, the drug may be held within a hydrophobic polymer matrix so that it is gradually leached out of the matrix upon contact with body fluids. Alternatively, the drug may be held within a hydrophilic matrix which gradually or rapidly dissolves in the presence of body fluid. The tablet core may comprise two or more layers having different release properties. The layers may be hydrophilic, hydrophobic or a mixture of hydrophilic and hydrophobic layers. Adjacent layers in a multilayer tablet core may be separated by an insoluble barrier layer or hydrophilic separation layer. An insoluble barrier layer may be formed of materials used to form the insoluble casing. A hydrophilic separation layer may be formed from a material more soluble than the other layers of the tablet core so that as the separation layer dissolves the release layers of the tablet core are exposed.

Suitable release rate controlling polymers include polymethacrylates, ethylcellulose, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, acrylic acid polymer, polyethylene glycol, polyethylene oxide, carrageenan, cellulose acetate, zein etc.

Suitable materials which swell on contact with aqueous liquids include polymeric materials include from cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high molecular weight hydroxypropylcellulose, carboxymethylamide, potassium methacrylatedivinylbenzene copolymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone and high molecular weight polyvinylalcohols.

The tablet core may comprise other conventional tableting ingredients, including diluents, disintegrants, lubricants, wetting agents, glidants, surfactants, release aids, colourants, gas producers, etc.

Suitable diluents include lactose, cellulose, dicalcium phosphate, sucrose, dextrose, fructose, xylitol, mannitol, sorbitol, calcium sulphate, starches, calcium carbonate, sodium carbonate, cellulose acetate, dextrates, dextrin, kaolin, lactitol, magnesium carbonate, magnesium oxide, maltitol, maltodextrin and maltose.

Suitable lubricants include magnesium stearate and sodium stearyl fumarate.

Suitable glidants include colloidal silica and talc.

Suitable wetting agents include sodium lauryl sulphate and docusate sodium.

A suitable gas producer is a mixture of sodium bicarbonate and citric acid.

The pharmaceutically active ingredient may be selected from a wide range of substances which may be administered orally. Suitable ingredients include acid-peptic and motility influencing agents, laxatives antidiarrhoeials, colorectal agents, pancreatic enzymes and bile acids, antiarrhythmics, antianginals, diuretics, anti-hypertensives, anti-coagulants, anti-thrombotics,

fibrinolytics, haemostatics, hypolipidaemic agents, anti-anaemia and neurotropenia agents, hypnotics, anxiolytics, anti-psychotics, anti-depressants, anti-emetics, anti-convulsants, CNS stimulants, analgesics, anti-pyretics, anti-migraine agents, non-steroidal anti-inflammatory agents, anti-gout agents, muscle relaxants, neuro-muscular agents, steroids, hypoglycaemic agents, hyperglycaemic agents, diagnostic agents, antibiotics, anti-fungals, anti-malarials, anti-virals, immunosuppressants, nutritional agents, vitamins, electrolytes, anorectic agents, appetite suppressants, bronchodilators, expectorants, anti-tussives, mucolytic, decongestants, anti-glaucoma agents, oral contraceptive agents, diagnostic and neoplastic agents.

The pharmaceutical active ingredient may be present in beads, membrane coated beads or microcapsules. The membrane can provide a delayed release function when in contact with physiological fluid, which enables the masking of undesirable taste; a sustained or slow release of active; protection from gastric fluid; targeted release of the actives along the gastro-intestinal tract such as stomach, jejenum, duodenum and the colon. The membrane may comprise of any pharmaceutically acceptable materials. Suitable membrane forming ingredients may include acacia, albumin, modified cellulose native and modified starches, sugars, wax, acrylic and methacrylic polymers.

The powder forming the coating may be applied by any suitable technique e.g. spraying, fluidised bed, falling curtain and electrostatic spraying. Electrostatic application is preferred.

The electrostatic application of powder material to a substrate is known. Methods have already been developed in the fields of electrophotography and electrography and examples of suitable methods are described, for example, in Electrophotography and Development Physics, Revised Second Edition, by L.B. Schein, published by Laplacian Press, Morgan Hill California. The electrostatic application of powder material to a solid dosage form is known and techniques are disclosed, for example, in GB9929946.3, WO92/14451,

WO96/35413, WO96/35516 and PCT/GB01/00425, and British Patent Application No. 9929946.3.

For example, WO92/14451 describes a process in which the cores of pharmaceutical tablets are conveyed on an earthed conveyor belt and electrostatically charged powder is deposited on the cores to form a powder coating on the surface of the cores.

A powder material for electrostatic application to a substrate should have certain properties. For example, the electrical properties of the powder material should be such as to make the powder material suitable for electrostatic application, and other properties of the powder material should be such that the material can be secured to the substrate once electrostatic application has taken place.

WO96/35413 describes a powder material which is especially suitable for electrostatic application to a poorly-conducting (non-metal) substrate such as a pharmaceutical tablet. Because it may be difficult to find a single component capable of providing the material with all the desired properties, the powder material comprises a number of different components which together are capable of providing the material with all or at least as many as possible of the desired properties, the components being co-processed to form "composite particles". For example, the powder material may comprise composite particles including one component which is fusible to form a continuous film on the surface of the substrate, and another component which has desirable electrical properties.

A potential disadvantage of the above mentioned powder materials, however, is that they are not readily adaptable to changes in formulation. The formulation of a powder material may be changed for a number of different reasons. For example, if the material is a coloured material, there may be a change in the colourant, or if the material is an active material, for example a physiologically active material there may be a change in the type of active material, or in the concentration of that active material. Because all the components of the powder material are intimately mixed, any change in the

components will alter the material's electrical properties and hence its performance in electrostatic application. Whenever there is a change in formulation, it may therefore be necessary, for optimum performance, to adjust the content of the component(s) that make the material suitable for electrostatic application, or perhaps even to use a different component.

PCT/GB01/00425 discloses a method of electrostatically applying a powder material to a substrate, wherein at least some of the particles of the material comprise a core and a shell surrounding the core, the core and the shell having different physical and/or chemical properties.

Where the particles of the powder material comprise a core and a shell surrounding the core, it is possible to place those components which are likely to be altered, for example colourant in the core, and to provide a more universal shell composition which is suitable for use with various core compositions, so that alterations may be made to the components that are in the core without substantially affecting the overall suitability of the powder material; thus, the shell ensures that the change in composition of the core does not affect the performance of the material in electrostatic application. Accordingly, alterations to one component of the powder material may be made with minimum alteration in the amounts of other components.

Generally, the powder material includes a component which is fusible, and that component may be present in the shell or in the core or in both the shell and the core. Advantageously, the fusible component is treatable to form a continuous film coating. Examples of suitable components are as follows: polyacrylates, for example polymethacrylates; polyesters; polyurethanes; polyamides, for example nylons; polyureas; polysulphones; polyethers; polystyrene; polyvinylpyrrolidone; biodegradable polymers, for example polycaprolactones, polyanhydrides, polylactides, polyglycolides, polyhydroxybutyrates and polyhydroxyvalerates; polyols, for example lactitol, sorbitol xylitol, galactitol and maltitol; sugars, for example sucrose, dextrose, fructose, xylose and galactose; hydrophobic waxes and oils, for example vegetable oils and hydrogenated vegetable oils (saturated and unsaturated fatty acids) e.g. hydrogenated castor oil, carnauba wax, and beeswax;

hydrophilic waxes; polyalkenes and polyalkene oxides; polyethylene glycol. Clearly there may be other suitable materials, and the above are given merely as examples. One or more fusible materials may be present. Preferred fusible materials generally function as a binder for other components in the powder.

In general the powder material should contain at least 30%, usually at least 35%, advantageously at least 80%, by weight of material that is fusible, and, for example, fusible material may constitute up to 95%, e.g. up to 85%, by weight of the powder. Wax, if present, is usually present in an amount of no more than 6%, especially no more than 3% by weight, and especially in an amount of at least 1% by weight, for example 1 to 6%, especially to 1 to 3%, by weight of the powder material.

Of the materials mentioned above, polymer binders (also referred to as resins) should especially be mentioned. Examples include polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate and methacrylate polymers, for example an ammonio-methacrylate copolymer, for example those sold under the name Eudragit.

Often resin will be present with a wax as an optional further fusible component in the core; the presence of a wax may, for example, be useful where fusing is to take place by a contact system for example using a heated roller, or where it is desired to provide a glossy appearance in the fused film. The fusible component may comprise a polymer which is cured during the treatment, for example by irradiation with energy in the gamma, ultra violet or radio frequency bands. For example, the core may comprise thermosetting material which is liquid at room temperature and which is hardened after application to the substrate.

Preferably, the powder material includes a material having a charge-control function. That functionality may be incorporated into a polymer structure, as in the case of Eudragit resin mentioned above, and/or, for a faster rate of charging, may be provided by a separate charge-control additive. Material

having a charge-control function may be present in the shell or in the core or in both shell and core. Examples of suitable charge-control agents are as follows: metal salicylates, for example zinc salicylate, magnesium salicylate and calcium salicylate; quaternary ammonium salts; benzalkonium chloride; benzethonium chloride; trimethyl tetradecyl ammonium bromide (cetrimide); and cyclodextrins and their adducts. One or more charge-control agents may be used. Charge-control agent may be present, for example, in an amount of up to 10% by weight, especially at least 1% by weight, for example from 1 to 2% by weight, based on the total weight of the powder material.

The powder material may also include a flow aid. The flow aid reduces the cohesive and/or other forces between the particles of the material to improve the flowability of the powder. Suitable flow aids (which are also known as "surface additives") are, for example, as follows: colloidal silica; metal oxides, e.g. fumed titanium dioxide, zinc oxide or alumina; metal stearates, e.g. zinc, magnesium or calcium stearate; talc; functional and non-functional waxes, and polymer beads, e.g. poly-methyl methacrylate beads, fluoropolymer beads and the like. Such materials may also enhance tribocharging. A mixture of flow aids, for example silica and titanium dioxide, should especially be mentioned. The powder material may contain, for example, 0 to 3% by weight, advantageously at least 0.1%, e.g. 0.2 to 2.5%, of surface additive flow aid.

Often the powder material includes a colourant and/or an opacifier. When the powder comprises a core and shell such components are preferably present in the core. Examples of suitable colourants and opacifiers are as follows: metal oxides, e.g. titanium dioxide, iron oxides; aluminium lakes, for example, indigo carmine, sunset yellow and tartrazine; approved food dyes; natural pigments. A mixture of such materials may be used if desired. Opacifier preferably constitutes no more than 50%, especially no more than 40%, more especially no more than 30%, for example no more than 10% by weight of the powder material, and may be used, for example, in an amount of at least 5% by weight of the powder. Titanium dioxide is an especially useful opacifier, providing white colour and having good hiding power and tinctorial strength.

Colourant present with opacifier may, for example, constitute no more than 10%, preferably from 1 to 5%, by weight of the powder. If there is no opacifier, the colourant may be, for example, 1 to 15%, e.g. 2 to 15%, especially 2 to 10%, by weight of the powder. To achieve optimum colour, amounts of up to 40% by weight of colourant may be needed in some cases, for example if inorganic pigments, e.g. iron oxides, are used. However, the powder material usually contains, for example, from 0 to 25% by weight in total of colourant and/or opacifier.

The powder material may also include a dispersing agent, for example a lecithin. The dispersing agent is preferably present with the colourant/opacifier (that is, preferably in the core), serving to improve the dispersion of the colourant and opacifier, more especially when titanium dioxide is used. The dispersing component is preferably a surfactant which may be anionic, cationic or non-ionic, but may be another compound which would not usually be referred to as a "surfactant" but has a similar effect. The dispersing component may be a co-solvent. The dispersing component may be one or more of, for example, sodium lauryl sulphate, docusate sodium, Tweens (sorbitan fatty acid esters), polyoxamers and cetostearyl alcohol. Preferably, the powder material includes at least 0.5%, e.g. at least 1%, for example from 2% to 5%, by weight of dispersing component, based on the weight of the powder material. Most often it is about 10% by weight of the colourant and opacifier content.

The powder material may also include a plasticiser, if necessary, to provide appropriate rheological properties. A plasticiser may be present in the core and/or the shell, but usually, if present, a plasticiser is included with resin used for the core to provide appropriate rheological properties, for example for preparation of the core by extrusion in a melt extruder. Examples of suitable plasticisers include polyethylene glycols, triethyl citrate, acetyltributyl citrate, acetyltriethyl citrate, tributyl citrate, diethyl phthalate, dibutyl phthalate, dimethyl phthalate, dibutyl sebacate and glyceryl monostearate.

A plasticiser may be used with a resin in an amount, for example, of up to 50% by weight of the total of that resin and plasticiser, the amount depending

inter alia on the particular plasticisers used. The powder may contain an amount of up to 50% by weight of plasticiser.

The powder coating material may further include one or more taste modifiers, for example aspartame, acesulfame K, cyclamates, saccharin, sugars and sugar alcohols or flavourings. Preferably there is no more than 5%, more preferably no more than 1%, of flavouring based on the weight of the powder material, but larger or smaller amounts may be appropriate, depending on the particular taste modifier used.

If desired the powder material may further include a filler or diluent. Suitable fillers and diluents are essentially inert and low cost materials with generally little effect on the colour or other properties of the powder. Examples are as follows: alginic acid; bentonite; calcium carbonate; kaolin; talc; magnesium aluminium silicate; and magnesium carbonate.

The particle size of the powder material has an important effect on the behaviour of the material in electrostatic application. Although materials having a small particle size are recognised as having disadvantages such as being more difficult to produce and to handle by virtue of the material's cohesiveness, such material has special benefits for electrostatic application and the benefits may more than counter the disadvantages. For example, the high surface to mass ratio provided by a small particle increase the electrostatic forces on the particle in comparison to the inertial forces. Increasing the force on a particle has the benefit of increasing the force that causes it to move into contact with the substrate, whilst a reduction in the inertia reduces the force needed to accelerate a particle and reduces the likelihood of a particle arriving at the substrate bouncing back off the substrate. However, very small particle sizes may not be achievable where the coating material comprises a high proportion of a particular ingredient, for example a high proportion of active material.

Preferably, at least 50% by volume of the particles of the material have a particle size no more than 100μm. Advantageously, at least 50% by volume of the particles of the material have a particle size in the range of 5μm to

40μm. More advantageously, at least 50% by volume of the particles of the material have a particle size in the range of 10 to 25μm.

Powder having a narrow range of particle size should especially be mentioned. Particle size distribution may be quoted, for example, in terms of the Geometric Standard Deviation ("GSD") ratios d_{90}/d_{50} or d_{50}/d_{10} where d_{90} denotes the particle size at which 90% by volume of the particles are below this figure (and 10% are above), d_{10} represents the particle size at which 10% by volume of the particles are below this figure (and 90% are above) , and d_{50} represents the mean particle size. Advantageously, the mean (d_{50}) is in the range of from 5 to 40μm, for example, from 10 to 25μm. Preferably, d_{90}/d_{50} is no more than 1.5, especially no more than 1.35, more especially no more than 1.32, for example in the range of from 1.2 to 1.5, especially 1.25 to 1.35, more especially 1.27 to 1.32, the particle sizes being measured, for example, by Coulter Counter or a laser particle size analyser. Thus, for example, the powder may have d_{50} = 10μm, d_{90} = 13μm, d_{10} = 7μm, so that d_{90}/d_{50} = 1.3 and d_{50}/d_{10} = 1.4.

The powder material is fusible so that it is treatable to form a continuous film coating.

It is important that the powder can be fused or treated without degradation of any active material in the powder and without degradation of the tablet core. For some materials it may be possible for the treatment step to involve temperatures up to and above 250°C. Preferably, however, the powder material is fusible at a pressure of less than 100lb/sq. inch, preferably at atmospheric pressure, at a temperature of less than 200°C, and most commonly below 150°C, and often at least 80°C, for example in the range of from 100 to 140°C

Fusing of the powder material may be carried out by any of a number of different fusing methods. The powder material is preferably fused by changing the temperature of the powder, for example by radiant fusing using electromagnetic radiation, for example infra red radiation or ultra-violet radiation, or conduction or induction, or by flash fusing. The amount of heat

required may be reduced by applying pressure to the powder material, for example by cold pressure fusing or hot roll fusing.

Preferably, the powder material has a glass transition temperature (Tg) in the range of 40°C to 120°C. Advantageously, the material has a Tg in the range of 50°C to 100°C. A preferred minimum Tg is 55°C, and a preferred maximum Tg is 70°C. Accordingly, more advantageously, the material has a Tg in the range of 55°C to 70°C. Generally, the powder material should be heated to a temperature above its softening point, and then allowed to cool to a temperature below its Tg.

If the dosage form is a rapid disintegrating tablet, the film formed by the powder material must be readily soluble in water.

The invention will now be described with reference to the accompanying drawing in which:

Figures 1 to 3 represent cross section through tablets in accordance with the invention,

Figure 4 represents a plot of weight loss against revolution for tablet cores and coated tablets tested in a friability tester and

Figure 5 represents a plot of weight loss against time for tablet cores and coated tablets tested on a shaker.

Figure 1 shows a tablet core 2 in the form of a circular biconvex tablet. The core is completely coated with a fused film 4.

Figure 2 illustrates a tablet core 2 of the same configuration as that in Figure 1. Coating 4 is applied to the two major surfaces 6 leaving the sidewall 8 uncovered. The coating provides complete protection to the major surfaces and limited protection to the edges of the tablet core.

Figure 3 shows a similar arrangement to Figure 2 with the coating 4 extending slightly along the sidewall 8 that regions 10 to provide additional protection to the edges of the tablet.

In the embodiments of Figures 2 and 3 different coatings may be applied to the major surfaces of the table core.

The invention will now be described with reference to the following Examples.

Example 1

A tablet core was formed by distribution of 20g a 5% w/w aqueous citric acid solution over a mixture of 360g of mannitol (Perlitol™) and 20g of sodium starch glycollate (Explotab™) using a planetary mixer (Kenwood Magimix 4100) and drying the resulting damp powder a forced air oven. The dried powder was blended with 4% cross-linked PVP (polyvinylpyrrolidine), Plolyplasdone XL-10, 1% of magnesium stearate, 0.5% aspartame and 0.1% lemon flavour and lightly compressed using 10mm diameter punches to give biconvex tablets of approximately 230mg by a Manesty F3 press.

A coat formulation was prepared by blending 68.6% PVP-VA copolymer, 10% methacrylic acid copolymer 4.4% PEG3000, 4.5% xylitol, 10% titanium dioxide and 2.5% ponceau 4R lake, melt extrusion of the mix using a EuroLab Extruder and micronisation of the extrudate.

The coat was applied by electrostatic deposition to each face of the table as in Figure 2 and the applied powder was fused using hot air at 160°C for 90 seconds. The fused coat was approximately 50µm thick.

The structural integrity of the tablets can be measured by radial tensile strength. This is determined by diametrical compression measurement. The test was carried out using a Schleuniger tester based on a counterweight principle. The tablet is placed between two anvils, a moving anvil driven by a speed-controlled electric motor presses the tablet against a stationary anvil. The maximal force which causes the tablet to fracture is then recorded and the radial tensile strength is calculated as described previously.

Tablet friability was determined according to standard US Pharmacopoeia method using a Copley friability tester. The tablets were weighed (6.5g) placed in a drum with an internal diameter between 283 and 291mm and a

depth between 36 and 40mm. One side of the drum is removable. The tablets were tumbled at each turn of the drum by a curved projection with an inside radius between 75.5 and 85.5 that extends from the middle of the drum to the outer wall. The drum is attached to the horizontal axis of a device that rotates at 25 ± 1rpm. At each turn, the tablets roll or slide and fall onto the drum wall or onto each other. After 100 revolutions i.e. 4 minutes, the intact tablets were collected, weighed and percentage weight loss (friability) was then calculated.

The properties of the tablet cores and coated tablets were as follows:

	Cores	Coated Tablets
tensile strength	18 N/cm^2	40 N/cm^2
friability weight loss	0.6%	0.8%
oral disintegration	16 seconds	22 seconds

The Example demonstrates a significant increase in tensile strength after the application of fusible coating.

During tablet manufacture and packaging, the surface of tablets may become eroded as they slide along the production line. This problem can become acute if the tablets are fragile and soft. A modified friability test was carried out by inclining the friability tester at 30° to the horizontal to give an indication of tablet erosion. Weight loss after up to 1000 revolutions was determined on both coated and uncoated tablets and the results are shown in Figure 4.

It is evident from Figure 4 that the uncoated tablets (tablet cores) erode as the test proceeds whereas the coated tablets slightly increase in weight as they pick up atmospheric moisture.

In another test for robustness, tablets were placed in a polypropylene container and shaken on the base of a Fritsch sieve shaker. This test is intended to simulate the shaking that tablets might experience when stored in a bottle or similar container. The weight loss of the tablets was measured at

10 minutes intervals and results are shown in Figure 5. The results again demonstrate the improved robustness of the tablets of this invention.

Example 2

Tablet cores were prepared by wet granulation of mannitol Perlitol™ (612g), microcrystalline cellulose Vivapur ™(200g), maize starch Aci-di-sol™ (50g), croscarmellose sodium Explotab™ (50g), sodium starch glycollate (50g), sodium lauryl sulphate (2g) with an aqueous solution of citric acid (30g), and the resulting wet mass was dried and passed through a 1mm screen. Magnesium stearate (5g) and colloidal silicon dioxide (1g) were blended into the screened granules, and then this blend (194g) was further blended with talc (6g). The resulting blend was lightly compressed on a Manesty F3 machine fitted with 10mm concave tooling.

Two coat formulations were prepared as follows.

Coat formulation A was prepared by blending 64.5% PVP-VA copolymer, 20% methacrylic acid copolymer 3% PEG3000, 10% titanium dioxide and 2.5% ponceau 4R lake, melt extrusion of the mix and micronisation of the extrudate.

Coat formulation B was prepared by blending 58.5% PVP-VA copolymer, 20% methacrylic acid copolymer, 9% PEG3000, 10% titanium dioxide and 2.5% ponceau 4R lake, melt extrusion of the mix and micronisation of the extrudate.

The tablets were coated as in Figure 1 by electrostatic deposition of coat A on one side of the tablet and fusing with air at 175°C for 180 seconds followed by electrostatic deposition of coat B on the second side of the tablet and fusing with air at 135°C for 270 seconds. The coats were approximately 50 microns thick.

The properties of the tablet cores and coated tablets were as follows:

	Cores	Coated Tablets
tensile strength	17 Ncm^2	70 N/cm^2
friability weight loss	1.5%	0.8%

Example 3

A soft tablet was prepared by combining two pre-prepared granules with other ancillary ingredients in a Y-cone blender, then compressed on a Manesty F3 machine with 10mm round concaved tooling. The tablet formulation is as follows:

Granule A:	1114.5g
Granule B:	360.0g
Aspartame:	7.5g
Lemon flavour:	3.0g
Magnesium stearate:	15.0g

The formation for granule A is:

Mannitol (Perlitol™)	2730g
Sodium starch glycollate (Explotab™)	120.0g
Citric acid	75.0g
Lactitol	75.0g

Citric acid and lactitol were dissolved in demineralised water to make a granulation solution , which was then used to granulate mannitol and sodium starch glycollate in a Diosna mixer. The wet mass was then dried in a Niro fluid bed drier at 60°C.

The formulation for granule B is:

Powdered mannitol	600.0g
Citric acid	5.0g
Lactitol	75.0g
Crospovidone (Polyplasdone™)	250.0g

Citric acid and lactitol were dissolved in demineralised water to make a granulation solution. Powdered mannitol and crospovidone were granulated in a planetary mixer and dried in a forced air oven at 60°C.

A coating formulation was prepared by blending 68.6% PVP-VA, 10% Eudragit™ (methacrylic acid copolymer), 4.4% PEG, 10% titanium dioxide, 4.5% xylitol and 2.5% ponceau 4R lake, melt extrusion of the mix and micronisation of the extrudate.

The coat was applied to the core by electrostatic deposition of the coating to the top and bottom of the tablet as shown in Figure 2. Variable weight of coating was applied to the core.

The properties of the tablets were as follows:

Coating thickness	0 microns (no coating)	28 microns	69 microns
Tensile strength	29 N/cm^2	58 N/cm^2	62 N/cm^2
Friability (USP)	0.7%	0.4%	0.5%

Example 4

The same core and coat formulations as in Example 3 were used to prepare coated tablets except that the tablet cores were prepared at lower hardness using the Manesty F3 tablet press. The coating was applied to the top and bottom of the tablet core by electrostatic coating and followed by fusion using hot air at 150°C for 90 seconds. The coating thickness was approximately 50 microns. The improvement in the integrity of the tablets of this invention is demonstrated by the increases in tensile strength as shown below:

	Uncoated tablet core	Coated and fused tablet
Tablet one	14 N/cm^2	51N/cm^2
Tablet two	21 N/cm^2	63 N/cm^2

Example 5

The same core formulations as in Examples 3 and 4 were used except that coatings of xylitol (Xylitab™) were applied onto the top and bottom of tablet core by compression coating using a Manesty F3 tablet press. The applied coatings were fused using hot air at 120°C for 90 seconds on each side. The improvement in the integrity of the tablets of this invention is demonstrated by the significant increase in tensile strength as shown below:

	Unfused	Fused
Tensile strength	20 N/cm^2	58 N/cm^2

CLAIMS

1. A pharmaceutical dosage form comprising:

a) a tablet core comprising a pharmaceutically active ingredient and one or more pharmaceutically active ingredient and one or more pharmaceutically acceptable adjuvants, the tablet core having a tensile strength of less than 38 N/cm^2 before coating and fusion and

b) a coating extending over at least 25% of the surface area of the tablet core, the coating resulting from deposition of a powder comprising fusible particles and fusing the particles to form a coating film, thereby providing the pharmaceutical dosage form with a greater hardness/crush strength than the tablet core.

2. A pharmaceutical dosage form as claimed in Claim 1 in which the tensile strength of the tablet core before coating is less than 30 N/cm^2 before coating and fusion.

3. A pharmaceutical dosage form as claimed in Claim 2 in which the tensile strength of the tablet core before coating and fusion is less than 22 N/cm^2.

4. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the coating covers from 50 to 100% of the surface area of the tablet core.

5. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the pharmaceutical dosage form has a tensile strength of at least 50 N/cm^2.

6. A solid pharmaceutical dosage form as claimed in Claim 5 in which the pharmaceutical dosage form has a tensile strength of at least 60 N/cm^2.

7. A solid pharmaceutical dosage form as claimed in Claim 6 in which the pharmaceutical dosage form has a tensile strength of at least 70 N/cm^2.

8. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core comprises two major opposing surfaces separated by a sidewall(s) at least the major surfaces being covered by the coating.

9. A solid pharmaceutical dosage form as claimed in Claim 8 in which at least a portion of the sidewall(s) is not covered by the coating.

10. A solid pharmaceutical dosage form as claimed in any preceding claim in which the tablet core has a circular cross-section.

11. A solid pharmaceutical dosage form as claimed in Claim 10 in which the tablet core comprises two convex major opposing surfaces.

12. A solid pharmaceutical dosage form as claimed in any preceding claim in which the tablet core comprises a binder selected from acacia, alginic acid, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydroxypropylmethylcellulose, magnesium aluminium silicate, Maltodextrin, methylcellulose, polyethylene oxide, povidone, sodium alginate and hydrogenated vegetable oils.

13. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core additionally comprises a release rate controlling polymer selected from polymethacrylates, ethylcellulose, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, acrylic acid polymer, polyethylene glycol, polyethylene oxide, carrageenan, cellulose acetate, glyceryl monostearate and zein.

14. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core additionally comprises a diluent selected from lactose, cellulose, dicalcium phosphate, sucrose, dextrose, fructose, xylitol, mannitol, sorbitol, calcium sulphate, starches, calcium carbonate, sodium carbonate,

cellulose acetate, dextrates, dextrin, kaolin, lactitol, magnesium carbonate, magnesium oxide, maltitol, maltodextrin and maltose.

15. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core comprises a hydrophobic matrix containing an active ingredient.

16. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core comprises a hydrophilic matrix containing an active ingredient.

17. A solid pharmaceutical dosage form as claimed in any preceding claim in which the tablet core is rapidly soluble or rapidly disintegratable.

18. A solid pharmaceutical dosage form as claimed in any preceding claim in which the active ingredient is selected from acid-peptic and motility influencing agents, laxatives, antidiarrhoeials, colorectal agents, pancreatic enzymes and bile acids, antiarrhythmics, antianginals, diuretics, anti-hypertensives, anti-coagulants, anti-thrombotics, fibrinolytics, haemostatics, hypolipidaemic agents, anti-anaemia and neurotropenia agents, hypnotics, anxiolytics, anti-psychotics, anti-depressants, anti-emetics, anti-convulsants, CNS stimulants, analgesics, anti-pyretics, anti-migraine agents, non-steroidal anti-inflammatory agents, anti-gout agents, muscle relaxants, neuro-muscular agents, steroids, hypoglycaemic agents, hyperglycaemic agents, diagnostic agents, antibiotics, anti-fungals, anti-malarials, anti-virals, immunosuppressants, nutritional agents, vitamins, electrolytes, anorectic agents, appetite suppressants, bronchodilators, expectorants, anti-tussives, mucolytes, decongestants, anti-glaucoma agents, oral contraceptive agents, diagnostic and neoplastic agents.

19. A solid pharmaceutical dosage form as claimed in Claim 18 in which the active is present in beads, membrane coated beads or microcapsules.

20. A solid pharmaceutical dosage form as claimed in Claim 19 in which the beads, membrane coated beads or microcapsules have a particle size in the range 50 to 1500 μm.

21. A solid dosage form as claimed in Claim 20 in which the beads, membrane coated beads or microcapsules have a particle size in the range 100 to 1000 μm.

22. A solid dosage form as claimed in Claims 19 to 21 in which the membrane has a function selected from taste masking function, an enteric protection function, a sustained release function to allow the release of an active from the dosage form over a sustained period of time and a controlled release function to allow the release of an active at targeted site along the gastrointestinal tract.

23. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the tablet core comprises a polymeric material which swells on contact with aqueous liquid, selected from cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high molecular weight hydroxypropylcellulose, carboxymethylamide, potassium methacrylatedivinylbenzene copolymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone and high molecular weight polyvinylalcohols.

24. A solid pharmaceutical dosage form as claimed in Claim 23 in which the tablet core disintegrates on contact with aqueous liquid.

25. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the coating is rapidly soluble in water.

26. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the coating comprises a polymer resin selected from polymethacrylates, cellulose and its derivatives, cellulose ethers and esters and cellulose acetate phthalate.

27. A solid pharmaceutical dosage form as claimed in any preceding Claim in which the coating additionally comprises one or more adjuvants selected from opacifiers, colourants, plasticisers and flow aids.

28. A solid pharmaceutical dosage form as claimed in Claim 27 in which the coating comprises a plasticiser selected from polyethylene glycols, triethyl

citrate, acetyltributyl citrate, acetyltriethyl citrate, tributyl citrate, diethyl phthalate, dibutyl phthalate, dimethyl phthalate, dibutyl sebacate and glyceryl monostearate.

29. A solid pharmaceutical dosage form as claimed in which the casing comprises a material having a charge control function.

30. A method of making a solid pharmaceutical dosage form as claimed in any preceding claim comprising the steps of:

(i) forming a tablet core comprising a pharmaceutically active ingredient and one or more pharmaceutically acceptable adjuvants, the tablet core having a tensile strength of less than 38 N/cm^2.

(ii) depositing a powder comprising fusible particles over at least 25% of the surface area of the tablet core and

(iii) heating the deposited powder to fuse the particles to form a coating film, thereby increasing the tensile strength of the dosage form.

31. A method as claimed in Claim 29 in which the tablet core is formed by compression of powder ingredients.

32. A method as claimed in Claim 30 in which the tablet core is formed by moulding.

33. A method as claimed in any one of Claims 30 to 32 in which the powder is applied by spraying, from a fluidised bed or a falling curtain of powder.

34. A method as claimed in any one of Claims 30 to 33 in which the powder is applied by electrostatic coating.

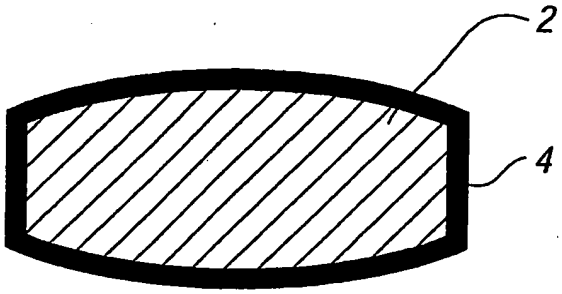


FIG. 1

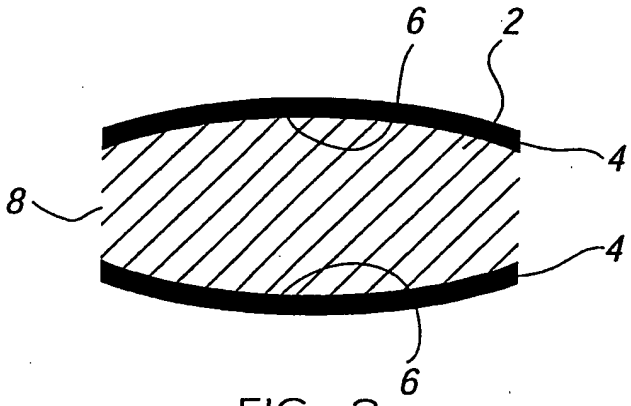


FIG. 2

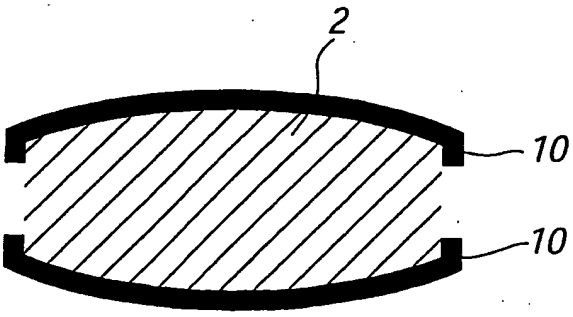
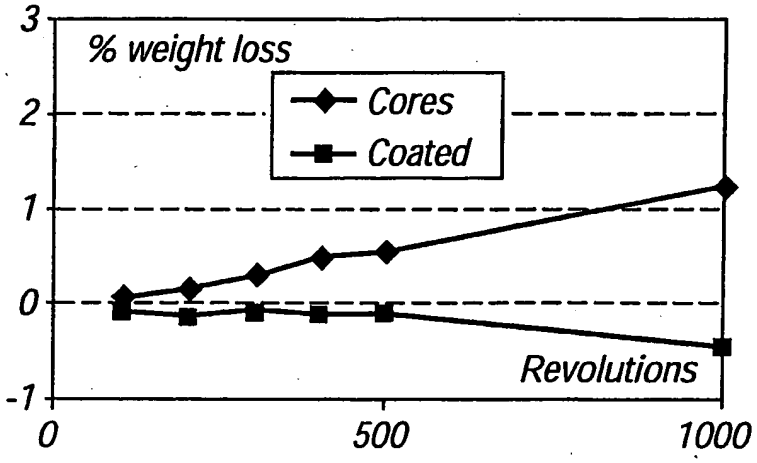


FIG. 3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2
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0
-1
% weight loss
Cores
Coated
Revolutions
0
500
1000

FIG. 4

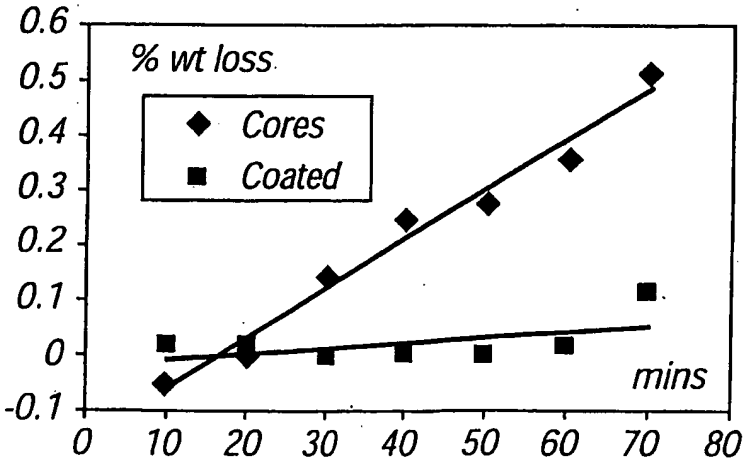
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
% wt loss
Cores
Coated
mins
0
10
20
30
40
50
60
70
80

FIG. 5

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/GB 03/00855

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 93 13758 A (PFIZER) 22 July 1993 (1993-07-22) page 5, line 4 - line 8; table 3	1-34
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2003	04/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Loher, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/GB 03/00855

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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